Pharmaceutical Compositions Comprising Epinastine For The Treatment of Skin Diseases

TECHNICAL FIELD

The present invention relates to new pharmaceutical compositions for the treatment of skin diseases. The compositions comprise an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof as a pharmacologically active compound and at least one further compound selected from the group consisting of a) sulfur containing amino acid(s) or peptide(s) as biologically active donor of a –S- or -SH group, b) vitamins of the B group, c) vitamins having antioxidant properties and d) antiphlogistic compounds. The compositions also may comprise pharmaceutically acceptable additives, carriers and excipients.

The invention also relates to the use of these formulations for the treatment of pruritus (itching) derived from skin disease such as urticaria, eczema, and skin irritation.

Remarkably, the compositions described in the present invention are highly effective in the treatment of skin diseases associated with allergic reactions.

BACKGROUND OF THE INVENTION

In recent years, the incidence of developing skin diseases associated with allergic reactions has increased due to changes in diet, changes of the life style, air pollution, increased exposure to environmental chemicals, from numerous environmental deterioration, stress in the social life and so on. Among these allergic reactions are urticaria, eczema, skin irritation, and dermatitis as well as skin diseases accompanying itching represented by pruritus, prurigo, psoriasis vulgaris, etc.

Urticaria, a synonym of wheal, is a transient edema. The disease is characterized by a sudden onset of itchy sensation on skin, followed by developing well defined eruption swelling up like weal and growing into a size of nail plate to palm exacerbated by scratching. Although the symptoms disappear within a couple of minutes to hours and

may not leave any skin disorder, episodes of development into eruption are likely to recur. Causes of urticaria may include autosensitization, sensitizations associated with difficult menstruation, pregnancy, foods, medicines and insect stings, abnormal responses to heat, cold, mechanical stimuli and light, remote responses to bacterial infections, gastrointestinal, hepatic, and renal disease, an endocrinopathic involvement, and psychological factors.

Eczema or dermatitis is the most major skin disease, characterized by inflammatory response on skin. Eczema and dermatitis are often referred altogether as eczematous dermatitis group. The diseases are often caused by pathological interactions caused by external stimuli (numbers of chemicals, fragrances, metals, detergents, medicines, plants, bacteria, insects, sunlight, heat, cold, dryness), internal abnormalities (local abnormalities such as perspiration, abnormal sebum secretion, abnormal keratosis, and systemic abnormalities such as atopic disposition, infection site, digestive disorder, renal dysfunction, endocrine disturbance), and bodily condition. Eczematous dermatitis group includes contact dermatitis, atopic dermatitis, seborrheic dermatitis, nummular eczema, autosensitization dermatitis, and lichen simplex chronicus Vidal.

Housewives' eczema, keratodermia tylodes palmaris progressiva, diaper dermatitis, and photocontact dermatitis are classified as atypical contact dermatitis. In addition, the group may include diffuse neurodermatitis, stasis dermatitis, infectious eczematoid dermatitis, and perioral dermatitis. Broadly, it may also include radiodermatitis, scald (burn), and frostbite.

Pruritus is a disease characterized by an onset of itchy sensation (itching) on apparently normal skin. Range of affected lesion divides pruritus into universal pruritus and localized pruritus. The disease is derived from a variety of causes, and often develops as a symptom of systemic disease.

Prurigo presents extreme itching and is papule or urticaria-like nodule that progress to chronic or recurrent disorder, and can be broadly classified into prurigo acuta including

strophulus infantum, lichen urticatus, prurigo aestiralis, prurigo simplex acuta, prurigo subacuta such as prurigo simplex subacuta, and prurigo chronica including chronica multiformis, prurigo nodularis, prurigo Hebra, and prurigo simplex chronica. Mechanisms of the pathogenesis are unrevealed. Insect sting in prurigo acuta, and diabetes mellitus, hepatopathy, leukemia, Hodgkin's disease, visceral cancer, and polycythemia in prurigo chronica are thought of as causatives.

Psoriasis vulgaris is an inflammatory skin disease, and presents histological characteristics of epidermal hyperplasia and inflammatory cellular infiltration. Eruption typically develops on head, extension side of extremities, and some parts of truncus which are in particular likely to come in contact with mechanical compression, in almost a half of which pruritus is observed. Immunological abnormalities may be concerned as a cause of disease.

It is emphasized that improvements on surroundings such as eliminating causative antigens is the most important treatment of these skin diseases, particularly for allergic skin disease. Nevertheless, as already reviewed, pathogenic causes are complicated, and therefore are fallible to be identified. Consequently, compositions combining antihistaminic compounds are of the frequent choice for treatments of these symptoms including itchy sensation caused from skin diseases.

Compositions comprising Epinastine in combination with vitamins of the B group have already been described.

Liquid-type formulations for cold and rhinitis combined with loxoprofen sodium, dihydrocodeine phosphate, Epinastine hydrochloride, dl- methylephedrine hydrochloride, ambroxol hydrochloride, anhydrous caffeine, vitamin B_1 nitrate, and vitamin B_2 as pharmacological active compounds are disclosed in Example 4 of Publication of Japanese Patent Application JP2001-199882A.

Liquid-type formulations for cold combined with loxoprofen sodium, dihydrocodeine phosphate, Epinastine hydrochloride, dl- methylephedrine hydrochloride, ambroxol hydrochloride, anhydrous caffeine, vitamin B_1 nitrate, and vitamin B_2 as pharmacological active compounds are disclosed in Example 4 of Publication of Japanese Patent Application JP2001-172175A.

Tablet-type antitussive agent for cold combined with ibuprofen, Epinastine hydrochloride, noscapine, benproperine phosphate, ambroxol hydrochloride, trimetoquinol hydrochloride, anhydrous caffeine, vitamin B_1 nitrate, and vitamin B_2 as pharmacological active compounds is disclosed in Example 4 of Publication of Japanese Patent Application JP10-017473A.

The aforementioned examples are combination medicines of Epinastine, vitamin B_1, vitamin B_2, etc. All these medicines are cold remedies.

Therefore, the use of a combination of Epinastine and a vitamin of the B group in the treatment of skin diseases in association with allergic reactions is new.

Compositions comprising Epinastine in combination with vitamins having antioxidant properties have also already been described.
A liquid antitussive formulation composed of acetaminophen, dimemorfan phosphate, Epinastine hydrochloride, dl-methylephedrine hydrochloride, bromhexine hydrochloride, lysozyme chloride, anhydrous caffeine, and vitamin C as pharmacological active compounds is disclosed in Example 5 of JP2001-097856A.

A liquid antitussive formulation composed of naproxen, dihydrocodeine phosphate, Epinastine hydrochloride, dl-methylephedrine hydrochloride, bromhexine hydrochloride, lysozyme chloride, anhydrous caffeine, and vitamin C as pharmacological active compounds is disclosed in Example 29 of JP2000-344682A.

A liquid medical composition having antitussive effect composed of fenoprofen, dihydrocodeine phosphate, Epinastine hydrochloride, dl-methylephedrine hydrochloride, bromhexine hydrochloride, lysozyme chloride, anhydrous caffeine, and vitamin C as pharmacological active compounds is disclosed in Example 5 of JP11-071281A.

A liquid cough medicine comprising fenoprofen, dihydrocodeine phosphate, Epinastine hydrochloride, dl-methylephedrine hydrochloride, ambroxol hydrochloride, anhydrous caffeine, and vitamin C as pharmacological active compounds is disclosed in Example 5 of JP11-071281A.

All these medicines comprising Epinastine and a vitamin with antioxidant properties are antitussive expectorant and cold remedies. The use thereof for the treatment of skin diseases has not been disclosed.

Compositions comprising Epinastine in combination with an antiphlogistic has already been disclosed.

A tablet formulation composed of phenylephrine hydrochloride, Epinastine hydrochloride, isopropamide iodide, glycyrrhizinate dipotassium, lidocaine hydrochloride, and anhydrous caffeine as pharmacological active compounds is disclosed in Example 3 of JP10-298107A.

This example is a combination drug composed of such as Epinastine and glycyrrhizinate dipotassium. The drug has extremely potent suppressive action on airway hypersecretion or cold syndrome therapeutic agent, and is not a treatment for skin disease.

SUMMARY OF THE INVENTION

The present invention aims to provide compositions for the treatment of skin diseases that exert its significant utility to achieve effective improvements.

In addition, the present invention intends to provide the compositions for treatment of skin diseases by employing highly effective pharmaceutical compounds for significant improvements on symptoms of skin diseases accompanying itching, particularly urticaria, eczema, skin fit, dermatitis, pruritus, eruption, and psoriasis vulgaris accompanying itchy sensation.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to pharmaceutical compositions for the treatment of skin disease, whereas the compositions comprise an antihistaminic-effective amount of Epinastine or a pharmaceutically acceptable salt thereof as pharmacologically active compound and at least one further compound selected from the group consisting of a) sulfur containing amino acid(s) or peptide(s), b) vitamins of the B group, c) vitamins having antioxidant properties and d) antiphlogistic compounds. Preferably, the vitamins having antioxidant properties are free radical scavenger.

Epinastine, (±) 3-amino-9, 13b-dihydro-1H-dibenz [c, f] imidazo [1,5-a] azepine, the hydrochloride thereof respectively, is a drug possessing H1-antihistaminic property. It primarily has been used to treat allergic reaction of the eyes and the nasal mucosa.

In all compositions of the present invention Epinastine preferably is taken in the form of a salt such as the hydrochloride, hydrobromide, oxalate, nitrate, sulfonate, fumarate, maleate, sulfate, and phosphate. The free base can be taken, too. Preferred is Epinastine-hydrochloride.

The amount of Epinastine or a pharmacologically acceptable salt thereof depends on the application route.

In the case of oral application, the daily dosage in equivalent quantity of Epinastine-hydrochloride for an adult is between 2 and 20 mg, preferably between 5 and 15 mg, and

further more preferably between 7.5 and 12.5 mg. preferably, this amount is given via one or more dosage units, like tablets.

In the case of topical application the amount in equivalent quantity of Epinastine hydrochloride is between 1 and 50 mg per 1 g of composition, preferably between 2 and 30 mg per 1 g of composition, and further more preferably between 5 and 15 mg per 1 g of composition.

In one embodiment of the invention, the pharmaceutical compositions for the treatment of skin diseases of the present invention comprise Epinastine and sulfur containing amino acid(s) or peptide(s).

The sulfur containing amino acid(s) or peptide(s) shall act as biologically active donor(s) of a –S- or a -SH group. Sulfur containing amino acids are known to maintain or activate enzyme activities and thereby exert a biochemical reaction in which the SH group is involved.

In the context of the present invention the sulfur containing amino acid(s) or peptide(s) can be used as such or in the form of a pharmaceutically acceptable salt or as derivatives thereof.

Examples of these sulfur containing amino acid(s) or peptide(s) comprise cysteine, methionine, aminoethylsulfonic acid (taurine), glutathione, cystine, homocysteine, homocystine, cysteine sulfinic acid, lanthionine, mixtures thereof as well as their pharmaceutically acceptable salts or derivatives. It is also possible to use the mixed disulfides of any of the aforementioned compounds having a thiol-group. However, homogeneous disulfides are preferred among the disulfides. It is preferred to use one or more of these acids, particularly preferred are cysteine, methionine, taurine and glutathione as well as their pharmaceutically acceptable salts or derivatives.

The amount of the sulfur containing amino acid varies in dependency of the type, the combination chosen and the application route.

For oral use the daily dosage for an adult lies in the range of from 5 to 10000 mg, and for topical use it lies in the range of from 0.01 to 200 mg.

L-Cysteine is one of the preferred sulfur containing amino acids to be used in the context of the present invention. For oral use the daily dosage for an adult lies normally in the range of from 5 to 1000 mg, preferably in the range of from 10 to 480 mg, and more preferably in the range of from 20 to 240 mg.

For topical use, the dosage is up to 200 mg per 1 g of composition, preferably between 0.01 and 50 mg per 1 g of composition, and more preferably between 0.1 and 15 mg per 1 g of composition.

L-Methionine is used in oral formulations in daily dosages for an adult of between 0.5 and 5000 mg, preferably between 1 and 3000 mg, and more preferably between 2 and 1000 mg.

For topical use the dosage is up to 200 mg per 1 g of composition, preferably between 0.01 and 50 mg per 1 g of composition, and more preferably between 0.1 and 15 mg per 1 g of composition.

Aminoethylsulfonic acid, known as taurine or 2-aminoethylsulfonic acid, is given in daily dosages for an adult if applied orally which are between 5 and 10000 mg, preferably between 25 and 5000 mg, and more preferably between 30 and 3000 mg.

For topical use the dosage is up to 200 mg per 1 g of composition, preferably between 0.01 and 50 mg per 1 g of composition, and more preferably between 0.1 and 15 mg per 1 g of composition.

Glutathione, γ-L-glutamyl-L-cysteinyl-glycine is given in daily dosages for an adult if applied orally which are between 5 and 1000 mg, preferably between 25 and 600 mg, an more preferably between 50 and 300 mg.

For topical use the dosage is up to 200 mg per 1 g of composition, preferably between 0.01 and 50 mg per 1 g of composition, and more preferably between 0.1 and 15 mg per 1 g of composition.

Dose adjustment of Epinastine and sulfur containing amino acid(s) or peptide(s) may reflect age, body weight, and manifesting symptoms.

Epinastine and the sulfur containing amino acid(s) or peptide(s) can be combined together in one pharmaceutical preparation or the two components are formulated separately from each other in two pharmaceutical preparations and then given together or in close timely proximity, i.e. within 12 hours, preferably within 1 hour more preferably within 15 minutes and in particular preferred within 2 minutes.
Preferred are pharmaceutical compositions that contain both ingredients, i.e. the both ingredients are not separated.

According to the invention there is also provided a pharmaceutical formulation for the treatment of skin diseases including at least one vitamin of the B group in addition to Epinastine. B group vitamins are regarded as a vitamin group having important influences on metabolism of protein, lipid, and carbohydrate by becoming components of coenzyme in the human vivo, or by being coenzyme itself, and help normalize the organism such as skin, nail, hair, and mucosa.

B group vitamins used in the pharmaceutical formulations for treatment of skin disease described in the present invention include vitamin-like active substances such as vitamin B_1 such as thiamine, thiamine hydrochloride, thiamine nitrate, thiamine disulfide nitrate, thiamine disulfide, thiamine dicetylsulfate salt, dicethiamine hydrochloride, fursultiamine hydrochloride, fursultiamine, octotiamine, cycotiamine, bisibutiamine, bisbentiamine,

prosultiamine, benfotiamine, cocarboxylase and dibenzoylthiamaine, and its salt and derivatives thereof, vitamin B_2 such as riboflavin, riboflavin butyrate, riboflavin sodium phosphate and flavin adenine dinucleotide, and its salt and derivatives thereof, vitamin B_6 such as pyridoxine, pyridoxal, pyridoxamine, pyridoxine phosphate, pyridoxal phosphate and pyridoxamine phosphate, and its salt and derivatives thereof, vitamin B_{12} such as cobalamin, cyanocobalamin, hydroxocobalamin, hydroxocobalamin acetate and mecobalamin, and its salt and derivatives thereof, niacin such as nicotinic acid, nicotinamide, inositol hexanicotinate and hepronicate, and its salt and derivatives thereof, pantothenic acid such as calcium pantothenate, sodium pantothenate, panthenol and pantethine, and its salt and derivatives thereof, biotin, vitamins such as folic acid, orotic acid such as orotic acid and choline orotate, and its salt and derivatives thereof, thioctic acid such as thioctic acid (lipoic acid) and thioctic acid amide, and its salt and derivatives thereof, p-aminobenzoic acid and its salt and derivatives thereof, inositol such as inositol and inositol hexanicotinate, and its salt and derivatives thereof, carnitine such as carnitine, carnitine chloride and acetyl-carnitine and its salt and derivatives thereof, and choline such as choline and choline orotate and its salt and derivatives thereof.

One or more compounds of these B group vitamins can be used to formulate this invention.

Preferred are the following combinations of Epinastine plus one vitamin of the vitamin B group:

Epinastine plus

vitamin B_1,

vitamin B_2,

vitamin B_6,

vitaminB_{12},

niacin,

pantothenic acid,

biotin,

folic acid,

orotic acid,
thioctic acid,
p-aminobenzoic acid,
inositol,
carnitine,
choline, or a salt or derivatives of each.

If the combination shall comprise at least two vitamins of the vitamin B group, the two vitamins preferably are:

- riboflavin or riboflavin butyrate and pyridoxine hydrochloride,
- thiamin nitrate and riboflavin or riboflavin butyrate,
- pyridoxine hydrochloride and thiamin nitrate,
- nicotinamide and pyridoxine hydrochloride,
- nicotinamide and thiamin nitrate,
- nicotinamide and riboflavin or riboflavin butyrate,
- pyridoxine hydrochloride and tocopherol acetate.

If the combination shall comprise at least three vitamins of the vitamin B group, the three vitamins preferably are:

- thiamin nitrate, riboflavin or riboflavin butyrate, pyridoxine hydrochloride,
- thiamin nitrate, riboflavin or riboflavin butyrate, nicotinamide,
- thiamin nitrate, nicotinamide, pyridoxine hydrochloride,
- nicotinamide, riboflavin or riboflavin butyrate, pyridoxine hydrochloride,
- pyridoxine hydrochloride, riboflavin sodium phosphate, panthenol.

If the combination shall comprise at least four vitamins of the vitamin B group, the four vitamins preferably are:
thiamin nitrate, riboflavin butyrate, pyridoxine hydrochloride, nicotinamide.

Of any of the named B vitamins another salt form may be used instead of the named one.

Furthermore, other pharmaceutical active substances may be combined to formulate this invention in addition to Epinastine and B group vitamins. Examples comprise of sulfur-containing amino acid such as cysteine, methionine, aminoethylsulfonic acid and glutathione, antioxidant vitamins such as vitamin C, vitamin E and vitamin A, antioxidant vitamin-like substances such as ubiquinone, pangamic acid and flavonoid, D group vitamins such as ergocalciferol and cholecalciferol.

Although combination amount of B group vitamins to formulate the present invention varies depending on types of B group vitamins, for oral use given daily to an adult it lies in the range from 0.0001 to 1500 mg, and for topical use it lies in the range from 0.1 to 200 mg/g.

In further details, combination amount of vitamin B_1 and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 0.1 to 500 mg, preferably in the range from 0.5 to 200 mg, and more preferably in the range from 1 to 100 mg, and for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of vitamin B_2 and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 0.5 to 180 mg, preferably in the range from 1 to 90 mg, and more preferably in the range from 2 to 45 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of vitamin B_6 and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 0.1 to 500 mg, preferably in the range from 1 to 200 mg, and more preferably in the range from 5 to 100 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of vitamin B_{12} and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 0.0001 to 15 mg, preferably in the range from 0.0005 to 3 mg, and more preferably in the range from 0.001 to 1.5 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of niacin and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 0.1 to 1000 mg, preferably in the range from 1 to 800 mg, and more preferably in the range from 12 to 400 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of pantothenic acid and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 0.1 to 120 mg, preferably in the range from 1 to 60 mg, and more preferably in the range from 5 to 30 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of biotin for oral use given daily to an adult lies normally in the range from 0.001 to 10 mg, preferably in the range from 0.005 to 1 mg, and more preferably in the range from 0.01 to 0.5 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of folic acid for oral use given daily to an adult lies normally in the range from 0.01 to 100 mg, preferably in the range from 0.05 to 20 mg, and more preferably in the range from 0.1 to 10 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of orotic acid and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 1 to 500 mg, preferably in the range from 5 to 200 mg, and more preferably in the range from 10 to 100 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of thioctic acid and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 0.1 to 500 mg, preferably in the range from 1 to 200 mg, and more preferably in the range from 2 to 100 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of p-aminobenzoic acid and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 1 to 1500 mg, preferably in the range from 2 to 1000 mg, and more preferably in the range from 10 to 500 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of inositol and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 1 to 800 mg, preferably in the range from 5 to 400 mg, and more preferably in the range from 10 to 200 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of carnitine and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 1 to 1000 mg, preferably in the range from 2 to 600 mg, and more preferably in the range from 10 to 100 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

Combination amount of choline and its salt and derivatives thereof for oral use given daily to an adult lies normally in the range from 1 to 1500 mg, preferably in the range from 2 to 1000 mg, and more preferably in the range from 10 to 500 mg. And for topical use it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, and more preferably in the range from 1 to 15 mg/g.

It is possible that the pharmaceutical formulations comprising Epinastine and one or more compounds of the vitamin B group are orally given all at once or in divided doses. For topical purposes the daily amount can be applied all at once or it can be divided in doses. The topical application should occur directly onto the affected region of skin. Dose adjustment of Epinastine and B group vitamins may reflect age, body weight, and manifesting symptoms.

In addition, when the pharmaceutical formulations comprising Epinastine and one or more compounds of the vitamin B group are orally given, part of or all of B group vitamins, may be formulated in a slow release form while Epinastine itself or a combination of Epinastine and B group vitamins are formulated for instant release. When other additional active components are present, they may be in either of the two formulation parts, the instant or the slow release part of the formulation in accordance with the pharmacokinetic characteristic of each active component.

Epinastine and the at least one vitamin of the B group can be combined together in one pharmaceutical preparation or the two combinations are formulated separately from each other in two pharmaceutical preparations and then given together or in close timely proximity, i.e. within 12 hours, preferably within 1 hour more preferably within 15 minutes and in particular preferred within 2 minutes.
Preferred are pharmaceutical compositions that contain both ingredients, i.e. the both ingredients are not separated.

These fast release components and slow release components may be present in one application unit each. The two components may be formulated separately and then they

are combined physically in one dosage unit, f. e. a capsule or the like or they are applied together. In an alternative embodiment the fast release components and slow release components may be regarded as one unit formulation. Such unit formulations may include for example multilayer tablets combining fast release layer(s) and slow release layer(s), granules combining fast release granules and slow release granules or capsules filled with the granules, hard capsules filled with a combination of small fast release tablet(s) and slow release tablet(s), and dry syrup or suspension syrup using microcapsule or microsphere as slow release components.

In a further embodiment of the present invention the pharmaceutical compositions for the treatment of skin diseases comprise at least one antioxidant vitamin in addition to Epinastine.

There is no particular restriction in types of the antioxidant vitamin(s) to be together with Epinastine provided that the corresponding vitamin(s) has (have) antioxidant properties.

In the context of the present invention preferred examples include vitamin C, vitamin E, vitamin A, and such vitamin-like active substances.

Concerning the vitamin C / vitamin C -like active substances, the at least one vitamin having antioxidant properties preferably may be selected from one or more of the following group: ascorbic acid, metallic ascorbate, such as sodium ascorbate, potassium ascorbate, calcium ascorbate, magnesium ascorbate, aluminum ascorbate, ascorbic acid derivative, such as ascorbyl phosphates, in particular sodium or potassium ascorbyl phosphate, magnesium ascorbyl phosphate, calcium ascorbyl phosphate, and aluminum ascorbyl phosphate, ascorbic sulfates such as disodium ascorbyl sulfate, potassium ascorbyl sulfate, magnesium ascorbyl sulfate, calcium ascorbyl sulfate, and aluminum ascorbyl sulfate, ascorbyl glucosides such as ascorbyl-2-glucoside, ascorbyl fatty acid glucosides, ascorbyl fatty acids, erythorbic acid (isoascorbic acid), and metallic erythorbate, such as sodium erythorbate.

Examples of vitamin E / vitamin E -like active substances comprise d-α-tocopherol, dl-α-tocopherol, d-α-tocopherol acetate, dl-α-tocopherol acetate, d-α-tocopherol succinate, dl-α-tocopherol succinate, dl-α-tocopherol calcium succinate, tocopherol nicotinate, vitamin E linoleate (preferably a mixture of tocopheryl esters, mainly tocopheryl linoleate), dl-βtocopherol, dl-γtocopherol, d-δ-tocopherol, and natural mixed tocopherol.

Examples of vitamin A / vitamin A -like active substances comprise vitamin A, retinal acetate, retinol palmitate, retinol etretinate, vitamin A oil, cod liver oil, strong cod liver oil, and also carotene such asα-carotene, β-carotene, γ-carotene, and lycopene can be added to the above.

Examples of other vitamin-like active substance which has antioxidant properties comprise of ubiquinone (coenzyme Q, ubidecarenone), pangamic acid, and flavonoids.

One or more compounds of these antioxidant vitamins can be used to formulate the antioxidant vitamin comprising composition of this invention. Preferably the composition contains only one of the named vitamins.

For combinations of Epinastine plus two vitamins the combinations with

- vitamin C plus vitamin E,
- vitamin C plus vitamin A, and
- vitamin C plus such vitamin-like active substances
- vitamin E plus vitamin A, and
- vitamin E plus such vitamin-like active substances

are preferred.

For combinations of Epinastine plus three vitamins the combinations with

- vitamin C, vitamin A and vitamin E

are preferred.

Furthermore, other pharmaceutical active substances can be combined with Epinastine and the antioxidant vitamins to formulate this invention. Examples comprise sulfur amino acids such as cysteine, methionine, aminoethylsulfonic acid or glutathione. Other examples are vitamin D such as ergocalciferol and cholecalciferol. However, the combination also may comprise any other kind of vitamin or vitamin mixture.

In the formulation comprising Epinastine and the antioxidant vitamin the amount of the at least one antioxidant vitamin varies depending on the type of the antioxidant vitamin. For daily oral use for an adult, it lies in the range of from 0.01 to 3000 mg, and for topical use, it lies in the range of from 0.1 to 200 mg/g.

In particular, the daily dosage range for a vitamin C, given orally to an adult lies in the range of from 5 to 3000 mg, preferably in the range of from 25 to 2000 mg, and more preferably in the range of from 50 to 500 mg, and for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 50 mg/g, and more preferably in the range of from 5 to 40 mg/g.

The daily dosage range for a vitamin E, given orally to an adult lies in the range of from 1 to 500 mg, preferably in the range of from 5 to 300 mg, and more preferably in the range of from 10 to 100 mg. And for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 60 mg/g, and more preferably in the range of from 0.5 to 30 mg/g.

The daily dosage range for a vitamin A, given orally to an adult lies in the range of from 10 to 10000 IU (international unit), preferably in the range of from 100 to 4000 IU, and more preferably in the range of from 500 to 2000 IU. And for topical use it lies in the range within 200000 IU/g, preferably in the range of from 100 to 50000 IU/g, and more preferably in the range of from 1000 to 10000 IU/g.

The daily orally to an adult given dosage range for ubiquinone, (coenzyme Q, ubidecarenone), which is vitamin-like active substance lies in the range of from 1 to 300

mg, preferably in the range of from 3 to 150 mg, and more preferably in the range of from 6 to 30 mg. And for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 50 mg/g, and more preferably in the range of from 1 to 15 mg/g.

The daily dosage range for a pangamic acid, given orally to an adult lies in the range of from 2 to 1000 mg, preferably in the range of from 10 to 500 mg, and more preferably in the range of from 20 to 100 mg. And for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 50 mg/g, and more preferably in the range of from 1 to 15 mg/g.

The daily dosage range for a flavonoid, given orally to an adult lies in the range of from 6 to 1500 mg, preferably in the range of from 30 to 600 mg, and more preferably in the range of from 60 to 300 mg. And for topical use it lies in the range within 200 mg/g, preferably in the range of from 0.1 to 50 mg/g, and more preferably in the range of from 1 to 15 mg/g.

It is possible that the pharmaceutical compositions comprising Epinastine and the antioxidant vitamin are given orally or topically all at once or in divided portions. Topically the formulation is applied directly onto the affected region of skin. Dose adjustment of Epinastine and antioxidant vitamins may reflect age, body weight, and manifesting symptoms.

In a further embodiment the pharmaceutical compositions for the treatment of skin diseases of the present invention comprise antiphlogistics in addition to Epinastine.

Antiphlogistics employed to formulate the present invention are preferably selected form the group of glycyrrhizinic acid (glycyrrhizin) and/or a salt thereof, glycyrrhetinic acid and/or a salt and/or derivative thereof, and/or tranexamic acid and/or a salt thereof. The inventive formulation may comprise one ore more of these antiphlogistics. Theses substances can be used as the neutral compounds or as pharmacologically acceptable salts.

Glycyrrhizinic acid, 20beta-carboxy-11-oxo-30-norolean-12-en-3beta-yl-2-O-beta-D-glucopyranuronosyl-alpha-D-glucopyranosid-uronic acid, is a natural triterpenoid saponine and is a drug that shows antiphlogistic efficacy in the treatment of detoxication, viral, allergic reactions and the like. It has glucocorticoid-like properties. Monomolecular Glycyrrhetinic acid, 3beta-hydroxy-11-oxoolean-12-en-30-oid acid and bimolecular glucuronic acid are other representatives of this chemical family with similar pharmacological properties.

Examples of pharmacologically acceptable salts of glycyrrhizinic acid include dipotassium glycyrrhizinate, potassium glycyrrhizinate, monoammonium glycyrrhizinate, di-ammonium glycyrrhizinate, and the like.

Moreover, examples of the derivatives of glycyrrhetinic acid include glyceryl glycyrrhetinate, stearyl glycyrrhetinate, and the like.

Tranexamic acid, trans-4-(aminomethyl)cyclohexanecarboxylic acid, is a drug showing anti-inflammatory effect, hemostatic action, and antiallergic action by preventing plasmin action.

The compositions comprising Epinastine and the antiphlogistic may also include other pharmacologically active substances such as group B vitamins and vitamin-like active substances such as vitamin B_1, vitamin B_6, vitamin B_{12}, niacin, pantothenic acid, biotin, folic acid, orotic acid, lipoic acid, p-aminobenzoic acid, inositol, carnitine, and choline, antioxidant vitamins and antioxidant vitamin-like substances such as vitamin C, vitamin E, vitamin A, ubiquinone, pangamic acid, and flavonoid, sulfur containing amino acid such as cysteine, methionine, aminoethylsulfonic acid, and glutathione, and vitamin D such as ergocalciferol and cholecalciferol - in addition to Epinastine and the antiphlogistic mentioned above.

Although the amount of the antiphlogistics in the inventive formulation may vary in dependency of the type of the antiphlogistic, the application route etc, the typical amount for oral use given daily to an adult lies in the range from 1 to 2000 mg, and for topical use it lies in the range from 0.1 to 200 mg/g.

Concerning glycyrrhizinic acid and its salt as well as glycyrrhetinic acid the amount for the inventive formulation for oral use given daily to an adult preferably is in the range from 1 to 800 mg, preferably in the range from 2 to 400 mg, more preferably in the range from 15 to 200 mg. For topical use, it lies normally in the range within 200 mg/g, preferably in the range from 0.1 to 50 mg/g, more preferably in the range from 0.2 to 20 mg/g.

Concerning tranexamic acid and its salt the amount for the inventive formulation for oral use given daily to an adult preferably is in the range from 10 to 2000 mg, preferably in the range from 100 to 1000 mg, more preferably in the range from 200 to 750 mg. For topical use, it lies normally in the range within 200 mg/g, preferably in the range from 1 to 50 mg/g, more preferably in the range from 5 to 20 mg/g.

The pharmaceutical compositions comprising Epinastine and the antiphlogistic may be orally given once or more times, and may be topically applied once or more times directly onto the affected legion of skin. The dose of Epinastine and/or the antiphlogistic may be adjusted in accordance with age, body weight, and manifesting symptoms.

In addition, when the pharmaceutical compositions comprising Epinastine and the antiphlogistic are orally given, the formulations may include a fast release component comprising Epinastine (or Epinastine and part of antiphlogistics) and a slow release component comprising part of or all of the antiphlogistic. When other additional active components are added, they may be added to slow release part and/or the fast release part of the formulation in accordance with the pharmacokinetic characteristic of each active component.

These fast release components and slow release components may be part of one single formulation (unit formulations) or they may be formulated separately in at least two independent formulations. Examples of such unit formulations may include multilayer tablets combining fast release layer(s) and slow release layer(s), granules combining fast release granules and slow release granules or capsules filled with the combination of granules, hard capsules filled with a combination of fast release tablet(s) and slow release tablet(s) both in small size, and dry syrup or suspension syrup using microcapsule or microsphere as slow release components.

All of the pharmaceutical compositions described in the present invention can be used in any oral form such as tablets, granules, fine granules, subtle granules, powders, capsules, caplets, soft capsules, pills, suspensions, emulsions, oral solutions, syrups, dried syrups, chewable forms, forming tablets, effervescent tablets, drops, orally disintegrable tablets, and oral fast-dispersing tablets, and in any topical form such as creams, ointments, gel ointments, suppositories, poultices, tapes, topical solutions, aerosols, lotions, and foams. In addition, preparation formed into microparticles such as microcapsule, nanocapsules, microspheres, nanospheres, liposomes may be also included in the aforementioned compositions.

Moreover, the properties of all of the inventive compositions of the present invention such as stability, release, continuance, disintegration, distinglation, dissolution, concealment of taste, improvement in usage etc. can be regulated by the addition of additives known in the art.

For example, the pharmaceutically active substance can be dispensed in separate granules, multi-layer granules, multi-layer tablets or dry coated tablets, tablets of separated granules, microcapsules, etc. Coating preparations such as sugarcoated tablets, film coating tablets, coating granule, effervescent pharmaceutical preparation can be used as well as chewable preparations, oral fast-dispersing preparations, in the mouth dissolving preparations, matrix preparations, together with comminutions, solid solutions, etc. Sweetening agents, refrigerants, antioxidants or stabilizing agents, agents adjusting a

certain pH-value can be added as well as the viscosity, the osmotic pressure or the salt concentration influencing agents. These methods can also be combined.

Optionally, also the following additives can be added: excipients, bases, binders, disintegrators, lubricants, superplasticizers, coating agents, sugar coating agents, plasticizers, antifoaming agents, polish, foaming agents, antistatic agents, desiccant, moisturizing agents, surfactant, solubilizer, buffer agents, resolvents, solubilizing agents, solvents, diluents, stabilizers, emulsifying agents, suspension, suspending agents, dispersing agents, isotonizing agents, aerosol propellant, adsorbents, reducing agents, antioxidant, backing, wetting agents, wet modifier, filler, extender, adhesives, viscous agent, softeners, pH modifiers, antiseptics, preservatives, sweetening agents or preferably bitter taste masking agents like sodium dodecylsulfate (sodium lauryl sulfate), corrigent, refrigerative agents, flavoring agents, perfume, fragrance, coloring matters, and the like. Any of these additives may be used in the regular compositions methods, and do not impose any limitation to such composition methods.

Examples of these additives are explained in the Japanese Pharmaceutical Excipients Directory 2000 (Japan Pharmaceutical Excipients Council edit, Yakuji Nippo. Ltd. issue).

These preparations can be manufactured in the usual manner, i.e. by adding preparation additives to the pharmacologically active substance.

The compositions described in the present invention are explained by examples which follow. However, the present invention of the pharmaceutical compositions is not limited to these examples.

EXAMPLES

Example 1

Powder

The following ingredients were homogeneously mixed. The resulted mixed particles were divided into portions of 600 mg to prepare powder compositions.

Epinastine hydrochloride	10 g
L-cysteine	240 g
Corn starch	590 g
Lactose	940 g
Magnesium stearate	20 g

Example 2

Tablet

The following ingredients were homogeneously mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 120 mg each.

Epinastine hydrochloride	30 g
L-cysteine	720 g
Lactose	690 g
Microcrystalline cellulose	684 g
Light anhydrous silicic acid	18 g
Talc	9 g
Magnesium stearate	9 g

Example 3

Tablet

The following ingredients were homogeneously mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 250 mg each.

Epinastine hydrochloride	20 g
L-methionine	400 g
Lactose	510 g
Microcrystalline cellulose	546 g
Light anhydrous silicic acid	12 g
Talc	6 g
Magnesium stearate	6 g

Example 4

Oral solution

The following ingredients were dissolved in sterile purified water, added with sodium hydrate to adjust at pH 5, and diluted with sterile purified water to get a total volume of 20 L. The resulted solution was transferred in portions of 50 mL into glass bottles to provide oral solutions.

Epinastine hydrochloride	4 g
Aminoethylsulfonic acid	400 g
Citric acid	50 g
Sodium citrate	10 g
Purified sucrose	2400 g
Caramel	60 g
Sodium hydrate	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount
Sterile purified water	Adequate amount

Example 5

Syrup

The following ingredients were dissolved in sterile purified water, added with citric acid to adjust at pH 2.5, and then diluted with sterile purified water to prepare syrup at the total volume of 10 L.

Epinastine hydrochloride	20 g
Glutathione	200 g
Purified sucrose	4000 g
Sodium chloride	30 g
Sodium citrate	20 g
Citric acid	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount

Sterile purified water	Adequate amount

Example 6

Sugarcoated tablet

The following ingredients were processed through a regular method to provide mixed particles, and the particle was compressed to form tablets at 240 mg each.

Epinastine hydrochloride	10 g
L-cysteine	240 g
Corn starch	675 g
Lactose	740 g
Microcrystalline cellulose	360 g
Hydroxypropylcellulose	90 g
Light anhydrous silicic acid	18 g
Talc	18 g
Magnesium stearate	9 g

Subsequently, the tablets were transferred into a coating pan, and coated using coating solution. The equal volume mixture of ethyl alcohol contained 5% weight/volume of hydroxypropylmethylcellulose and purified water to increase in weight/volume by 10 mg per one tablet. Next, 2% weight/volume of talc, 2% weight/volume of titanium oxide, 3% weight/volume of calcium carbonate, 1% weight/volume of powdered acacia, and aqueous solution containing 60% weight/volume of purified sucrose were used to coat tablets to give increase in weight/volume by 150 mg per one tablet. Finally, aqueous solution containing 60% weight/volume purified sucrose was used to coat tablets to give an increase in weight/volume by 30 mg per one tablet. Thus sugarcoated tablets were prepared.

Example 7

Granules

The following ingredients were prepared as granules through a regular method to prepare mixed particles, and packed to give an amount of 1000 mg per one pack for granules.

Epinastine hydrochloride	10 g
DL-methionine	1000 g
Calcium carboxymethylcellulose	240 g
Mannitol	1100 g
Corn starch	508 g
Tartaric acid	100 g
Aspartame	20 g
Acesulfame potassium	20 g
Fragrant materials	2 g

Example 8

Cream

The following ingredients were processed through a regular method to form a cream of a total weight of 1kg, added with sodium citrate to adjust at pH 5.

Epinastine hydrochloride	10.0 g
L-cysteine	1.0 g
Medium chain fatty acid triglyceride	200.0 g
Propylene glycol	150.0 g
Glyceryl monostearate	80.0 g
Polyoxyethylene cetyl ether	40.0 g
Diisopropyl adipate	50.0 g
Citric acid	0.1 g
Sodium citrate	Adequate amount
Antiseptics	Adequate amount
Purified water	Adequate amount

Any of the following examples 9 to 16 may comprise a sweetener or preferably a bitter taste masking agent, like for example sodium dodecylsulfate (sodium lauryl sulfate) in an amount of less than 300 mg for a daily dosage.

Example 9

Powder

The following ingredients were homogeneously mixed. The resulted mixed particles were divided into portions of 800 mg to prepare powder compositions.

Epinastine hydrochloride	20.0 g
Riboflavin	24.0 g
Pyridoxine hydrochloride	100.0 g
Calcium pantothenate	60.0 g
L-cysteine	320.0 g
Biotin	0.1 g
Orotic acid	400.0 g
Thioctic acid amide	20.0 g
p-Aminobenzoic acid	600.0 g
Corn starch	1167.9 g
Lactose	2040.0 g
Magnesium stearate	48.0 g

Example 10

Tablet

The following ingredients were homogeneously mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 150 mg each.

Epinastine hydrochloride	30 g
Thiamin nitrate	45 g
Riboflavin butyrate	36 g
Pyridoxine hydrochloride	135 g
Nicotinamide	450 g
Calcium pantothenate	90 g
Lactose	933 g
Microcrystalline cellulose	945 g
Light anhydrous silicic acid	18 g
Talc	9 g

Magnesium stearate	9 g

Example 11

Tablet

The following ingredients were homogeneously mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 250 mg each.

Epinastine hydrochloride	20 g
Pyridoxal phosphate	24 g
Riboflavin butyrate	24 g
Inositol	36 g
Aminoethyl sulfonic acid	72 g
Panthenol	120 g
Carnitine chloride	100 g
Biotin	1 g
Folic acid	20 g
Lactose	513 g
Microcrystalline cellulose	546 g
Light anhydrous silicic acid	12 g
Talc	6 g
Magnesium stearate	6 g

Example 12

Oral solution

The following ingredients were dissolved in sterile purified water, added with sodium hydrate to adjust at pH 5, and diluted with sterile purified water to get a total volume of 20 L. The resulted solution was transferred in portions of 50 mL into glass bottles to provide oral solutions.

Epinastine hydrochloride	4 g
Aminoethylsulfonic acid	80 g
Inositol	20 g
Thiamin nitrate	4 g

Riboflavin sodium phosphate	4 g
Pyridoxine hydrochloride	4 g
Carnitine chloride	40 g
Nicotinamide	10 g
Calcium pantothenate	8 g
Orotic acid choline	40 g
Cyanocobalamin	0.004 g
Thioctic acid	2 g
Citric acid	50 g
Sodium citrate	10 g
Purified sucrose	2400 g
Caramel*	60 g
Sodium hydrate	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount
Sterile purified water	Adequate amount

* instead of Caramel sodium dodecylsulfate in an amount of up to 300 mg per day may be used.

Example 13

Syrup

The following ingredients were dissolved in sterile purified water, added with citric acid to adjust at pH 2.5, and then diluted with sterile purified water to prepare syrup at the total volume of 10 L.

Epinastine hydrochloride	20 g
Pyridoxine hydrochloride	20 g
Riboflavin sodium phosphate	40 g
Panthenol	60 g
Purified sucrose	4000 g
Sodium chloride	30 g

Sodium citrate	20 g
Citric acid	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount
Sterile purified water	Adequate amount

Example 14

Sugarcoated tablet

The following ingredients were processed through a regular method to provide mixed particles, and the particle was compressed to form tablets at 250 mg each.

Epinastine hydrochloride	10 g
Calcium pantothenate	15 g
Ascorbic acid	200 g
L-cysteine	160 g
Corn starch	630 g
Lactose	740 g
Microcrystalline cellulose	360 g
Hydroxypropylcellulose	90 g
Light anhydrous silicic acid	18 g
Talc	18 g
Magnesium stearate	9 g

Subsequently, the tablets were transferred into a coating pan, and coated using coating solution. The equal volume mixture of ethyl alcohol contained 5% weight/volume of hydroxypropylmethylcellulose and purified water to increase in weight/volume by 10 mg per one tablet. Next, 2% weight/volume of talc, 2% weight/volume of titanium oxide, 3% weight/volume of calcium carbonate, 1% weight/volume of powdered acacia, and aqueous solution containing 60% weight/volume of purified sucrose were used to coat tablets to give increase in weight/volume by 150 mg per one tablet. Finally, aqueous solution containing 60% weight/volume purified sucrose was used to coat tablets to give

an increase in weight/volume by 30 mg per one tablet. Thus sugarcoated tablets were prepared.

Example 15

Granules

The following ingredients were prepared as granules through a regular method to prepare mixed particles, and packed to give an amount of 1000 mg per one pack for granules.

Epinastine hydrochloride	10 g
Thiamin nitrate	5 g
Riboflavin	5 g
Pyridoxine hydrochloride	10 g
Nicotinamide	10 g
DL-methionine	1000 g
Calcium carboxymethylcellulose	240 g
Mannitol	1100 g
Corn starch	478 g
Tartaric acid	100 g
Aspartame*	20 g
Acesulfame potassium	20 g
Fragrant materials	2 g

*instead of aspartame sodium dodecylsulfate in an amount of up to 300 mg per day may be used.

Example 16

Cream

The following ingredients were processed through a regular method to form a cream of a total weight of 1kg, added with sodium citrate to adjust at pH 5.

Epinastine hydrochloride	10.0 g
Pyridoxine hydrochloride	1.0 g
Tocopherol acetate	10.0 g

Medium chain fatty acid triglyceride	200.0 g
Propylene glycol	150.0 g
Glyceryl monostearate	80.0 g
Polyoxyethylene cetyl ether	40.0 g
Diisopropyl adipate	50.0 g
Citric acid	0.1 g
Sodium citrate	Adequate amount
Antiseptics	Adequate amount
Purified water	Adequate amount

Example 17

Powder

The following ingredients were uniformly mixed. The resulted mixed particles were divided into 600 mg per one pack to prepare powder compositions.

Epinastine hydrochloride	10 g
Calcium ascorbate	180 g
L-cysteine	160 g
Corn starch	530 g
Lactose	900 g
Magnesium stearate	20 g

Example 18

Granules

The following ingredients were prepared into granules through a regular method to prepare mixed particles, and packed to give amount of 1000 mg per one pack for granules.

Epinastine hydrochloride	10 g
Ascorbic acid	250 g
Calcium ascorbate	250 g
Riken Dry A-S200PT (Vitamin A 200,000 I.U./g)	0.01 g
dl- α-tocopherol calcium succinate	100 g

Ubiquinone	30 g
Pangamic acid	50 g
Flavonoid	100 g
Calcium carboxymethylcellulose	240 g
Mannitol	1300 g
Corn starch	527.99 g
Tartaric acid	100 g
Aspartame	20 g
Acesulfame potassium	20 g
Fragrant materials	2 g

Example 19

Tablet

The following ingredients were uniformly mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 250 mg each.

Epinastine hydrochloride	30 g
dl- α-tocopherol calcium succinate	250 g
Ubiquinone	75 g
Lactose	310 g
Microcrystalline cellulose	575 g
Light anhydrous silicic acid	5 g
Talc	5 g
Magnesium stearate	5 g

Example 20

Tablet

The following ingredients were uniformly mixed. The resulted mixed particles were compressed with a mold to prepare tablets at 250 mg each.

Epinastine hydrochloride	20 g
Ascorbic acid	200 g
dl- α -tocopherol calcium succinate	200 g

Riken Dry A-S200PT (Vitamin A 200,000 I.U./g)	0.02 g
Lactose	455.98 g
Microcrystalline cellulose	600 g
Light anhydrous silicic acid	12 g
Talc	6 g
Magnesium stearate	6 g

Example 21

Oral solution

The following ingredients were dissolved into a portion of sterile purified water, added with sodium hydrate to adjust at pH 5, and diluted with sterile purified water to make total volume of 20 L. The resulted solution was transferred by 50 mL into glass bottles to provide oral solutions.

Epinastine hydrochloride	4 g
Ascorbic acid	40 g
Aminoethylsulfonic acid	400 g
Citric acid	50 g
Sodium citrate	10 g
Purified sucrose	2400 g
Caramel	60 g
Sodium hydrate	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount
Sterile purified water	Adequate amount

Example 22

Cream

The following ingredients were processed through a regular method to form cream at the total weight of 1kg, added with sodium citrate to adjust at pH 5.

Epinastine hydrochloride	10.0 g
dl- a-tocopherol acetate	5.0 g

Vitamin A oil: vitamin A 100000 I.U./g	2.0 g
Medium chain fatty acid triglyceride	200.0 g
Propylene glycol	150.0 g
Glyceryl monostearate	80.0 g
Polyoxyethylene cetyl ether	40.0 g
Diisopropyl adipate	50.0 g
Citric acid	0.1 g
Sodium citrate	Adequate amount
Antiseptics	Adequate amount
Purified water	Adequate amount

Example 23

Tablet

The following ingredients were homogeneously mixed. The resulting mixed particles were compressed with a mold to prepare tablets of 250 mg each.

Epinastine hydrochloride	20 g
Potassium glycyrrhizinate	360 g
Pyridoxine hydrochloride	45 g
Nicotinamide	450 g
Calcium pantothenate	60 g
Lactose	481 g
Microcrystalline cellulose	506 g
Light anhydrous silicic acid	14 g
Magnesium stearate	10 g
Talc	4 g

Example 24

Powder

The following ingredients were homogeneously mixed. The resulted mixed particles were divided into portions of 600 mg to prepare powder compositions.

Epinastine hydrochloride	5 g

Tranexamic acid	375 g
Corn starch	238 g
Lactose	270 g
Magnesium stearate	12 g

Example 25

Two layer tablet comprising an A layer and a B layer

The following ingredients of A layer and B layer were processed according to a standard method to provide mixed particles, respectively, and the particles were compressed to form two layer tablet at 250 mg (A layer 100 mg, B layer 150 mg) each.

A layer	
Epinastine hydrochloride	60 g
Lactose	258 g
Microcrystalline cellulose	270 g
Light anhydrous silicic acid	6 g
Talc	3 g
Magnesium stearate	3 g
B layer	
Monoammonium glycyrrhizinate	360 g
Pyridoxine hydrochloride	72 g
Lactose	330 g
Hydrogenated oil	84 g
Hydroxypropylmethylcellulose 2208	45 g
Magnesium stearate	9 g

Example 26

Oral solution

The following ingredients were dissolved in sterile purified water, added with sodium hydrate to adjust at pH 5, and diluted with sterile purified water to get a total volume of 20 L. The resulted solution was transferred in portions of 50 mL into glass bottles to provide oral solutions.

Epinastine hydrochloride	4 g
Glycyrrhizinic acid	40 g
Aminoethylsulfonic acid	80 g
Inositol	20 g
Thiamin nitrate	4 g
Riboflavin sodium phosphate	4 g
Pyridoxine hydrochloride	4 g
Carnitine chloride	40 g
Nicotinamide	10 g
Calcium pantothenate	8 g
Citric acid	50 g
Sodium citrate	10 g
Purified sucrose	2400 g
Caramel	60 g
Sodium hydrate	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount
Sterile purified water	Adequate amount

Example 27

Syrup

The following ingredients were dissolved in sterile purified water, added with citric acid to adjust a pH of 2.5. Then they were diluted with sterile purified water to prepare syrup at the total volume of 10 L.

Epinastine hydrochloride	20 g
Dipotassium glycyrrhizinate	220 g
Pyridoxine hydrochloride	20 g
Riboflavin sodium phosphate	40 g
Panthenol	60 g
Purified sucrose	4000 g
Sodium chloride	30 g

Sodium citrate	20 g
Citric acid	Adequate amount
Antiseptics	Adequate amount
Flavor	Trace amount
Sterile purified water	Adequate amount

Example 28

Sugarcoated tablet

The following ingredients were processed according to a standard method to provide mixed particles, and the particle was compressed to form tablets at 240 mg each.

Epinastine hydrochloride	10 g
Dipotassium glycyrrhizinate	200 g
L-cysteine	120 g
Ascorbic acid	100 g
Pyridoxine hydrochloride	50 g
Calcium pantothenate	30 g
Riboflavin butyrate	12 g
Lactose	640 g
Corn starch	406 g
Microcrystalline cellulose	306 g
Low substituted hydroxypropylcellulose	130 g
Hydroxypropylcellulose	90 g
Light anhydrous silicic acid	45 g
Talc	12 g
Magnesium stearate	9 g

Subsequently, the tablets were transferred into a coating pan, and coated using coating solution. The equal volume mixture of ethyl alcohol contained 5% weight/volume of hydroxypropylmethylcellulose and purified water to increase in weight/volume by 10 mg per one tablet. Next, 2% weight/volume of talc, 2% weight/volume of titanium oxide, 3% weight/volume of calcium carbonate, 1% weight/volume of powdered acacia, and

aqueous solution containing 60% weight/volume of purified sucrose were used to coat tablets to give increase in weight/volume by 100 mg per one tablet. Finally, aqueous solution containing 60% weight/volume purified sucrose was used to coat tablets to give an increase in weight/volume by 100 mg per one tablet. Thus sugarcoated tablets were prepared.

Example 29

Granules

The following ingredients were prepared as granules according to a standard method to prepare mixed particles, and packed to give an amount of 1000 mg per one pack for granules.

Epinastine hydrochloride	10 g
Glycyrrhizinic acid	90 g
Thiamin nitrate	5 g
Riboflavin	5 g
Pyridoxine hydrochloride	6 g
Nicotinamide	30 g
Orotic acid	90 g
Hesperidin	120 g
DL-methionine	100 g
Calcium carboxymethylcellulose	240 g
Mannitol	1500 g
Corn starch	662 g
Tartaric acid	100 g
Aspartame	20 g
Acesulfame potassium	20 g
Fragrant materials	2 g

Example 30

Cream

The following ingredients were processed according to a standard method to form a

cream of a total weight of 1kg, added with sodium citrate to adjust at pH 5.

Epinastine hydrochloride	10.0 g
Glycyrrhetinic acid	10.0 g
Pyridoxine hydrochloride	1.0 g
Medium chain fatty acid triglyceride	200.0 g
Propylene glycol	150.0 g
Glyceryl monostearate	80.0 g
Polyoxyethylene cetyl ether	40.0 g
Diisopropyl adipate	50.0 g
Citric acid	0.1 g
Sodium citrate	Adequate amount
Antiseptics	Adequate amount
Purified water	Adequate amount

Example 31

Ointment

The following ingredients were processed according to a standard method to form an ointment of a total weight of 1kg.

Epinastine hydrochloride	10 g
Glycyrrhetinic acid	10 g
Crotamiton	100 g
Lidocaine	20 g
Chlorhexidine hydrochloride	2 g
Paraffin	40 g
Cetanol	30 g
White beeswax	30 g
White petrolatum	Adequate amount